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Pronamide
Position Document 1

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Pronamide Working Group
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16. Abstract (Limit: 200 words)

Preliminary Risk Assessment: Examination of possible unreasonable risks associated with uses of pesticide and a gathering of all available information to determine whether or not this or any other risk does exist. Initiates literature search and evaluates risk data. Limited information on exposure to forecast extent of risk.

It is also included

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Pronamide: Position Document 1

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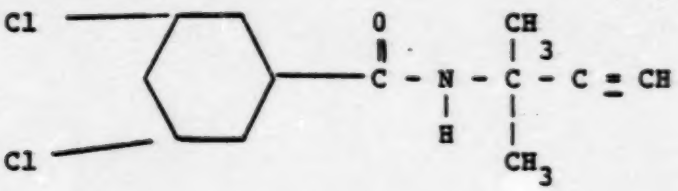
I. Background

A. General Chemistry

Pronamide (N-(1,1-dimethyl-2-propynl)3,5-dichlorobenzamide) was patented as a herbicide in 1964 by Dr. A. Crovetti of Abbott Laboratories, Northbrook, Ill.[1/] The proprietary rights to the compound were transferred to Rohm and Haas Company, Inc., in 1968. Abbott Laboratories still receives a royalty from Rohm and Haas from pronamide production.

There are no currently registered pesticides that are chemically similar to pronamide. Rohm and Haas has indicated that pronamide is probably the most biologically active compound of its type (1).



Pronamide

Physical characteristics of this compound are:

Melting Point	155°C
Solubility in H^2O	15 ppm
Vapor Pressure	8.5×10^{-5} mm

[1/] U.S. Patents 3,534,098 and 3,640,699 granted on October 13, 1970, and February 8, 1972.

Pronamide is synthesized as a solid. The technical chemical is packaged as a coarse powder formulation. Pronamide products that are ready for application are wettable powders or granules.

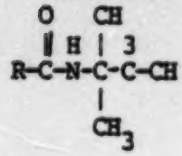
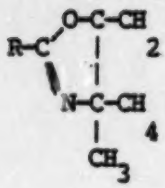
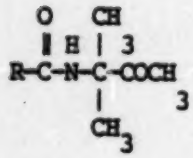
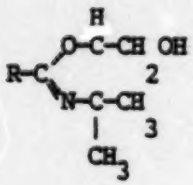
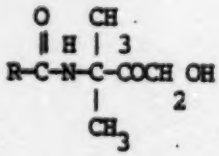
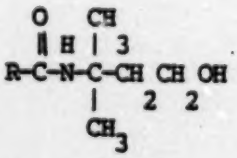
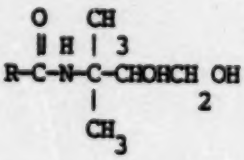
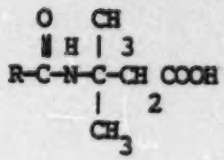
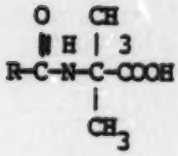
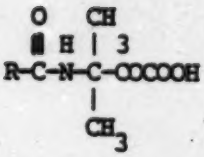
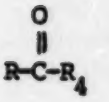
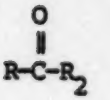
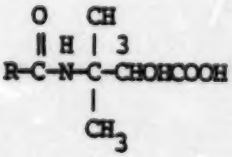
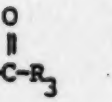
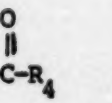
B. Residue Chemistry

In a study of pronamide metabolism, cows and rats fed pronamide excreted over half the amount they ingested directly through the gastrointestinal tract in the feces. Radioisotope studies in the cows and rats indicated that only a slight percentage of the ingested pronamide is metabolized in the gastrointestinal tract. However, once pronamide is absorbed through the intestinal lining, at least seven metabolites can be identified in the urine (2).

Pronamide metabolism in mammals is similar to fatty acid metabolism in that the aliphatic chain is modified by a series of carboxylic acid transformations. Since these chemical transformations follow fatty acid metabolism, which is a liver function, pronamide metabolism may also largely be a function of the liver.

Metabolism of pronamide by plants was demonstrated by Yih and Swithenbank in 1971 (3). A plant study using alfalfa revealed that at least ten metabolites could be

FIGURE 1. Pronamide Metabolites

Metabolite No.	Structure
Compound A (Pronamide)	
I	
II	
III	
IV	
V	
VI	
VII	
VIII	
IX	
X	
XI	
XII	
XIII	
XIV	

$R_1R_2R_3R_4$ are unknown

TABLE 1. Occurrence of Pronamide Metabolites in Soil, Plants, and Mammals

Metabolite	Media				
	Soil	Alfalfa	Rat Feces	Rat Urine	Cow Urine
Pronamide	+	+	+	+	-
I	+	+	+	-	-
II	+	+	+	-	-
III	+	+	+	+	-
IV	+	+	+	+	-
V	+	+	+	-	-
VI	+	+	+	+	-
VII	+	+	+	+	+
VIII	+	+	+	+	+
IX	+	+	-	-	-
X	-	+	-	-	-
XI	-	-	+	+	-
XII	-	-	-	+	+
XIII	-	-	-	+	+
XIV	-	-	-	-	+

NOTE: Structures of the metabolites are given in Figure 1.

+ = present
- = absent

Sources: Appendices 3 and 4.

identified in the alfalfa tissue after treatment with pronamide. This study indicated that the treated crop should not be harvested until 120 days after the last pronamide application. A list of pronamide metabolites and media in which they occur may be found in Figure 1 and Table 1.

C. Environmental Chemistry

Soil degradation patterns of pronamide follow pathways similar to the metabolic pathways found in plants and animals. Residues of pronamide in soil were detectable in amounts of 0.27 ppm for up to 112 days after field application (3). In a study using ^{14}C-pronamide, Fisher found that 13% of the pronamide changed to $^{14}CO_2$ after 33 days. Fisher speculates that this change was accomplished by soil bacteria since there was no significant $^{14}CO_2$ liberation in a similar test in sterilized soil (4).

Walker (5), Yih et al. (6), and Leistra et al. (7) conducted additional studies of the persistence of pronamide in soil. All of these studies indicated that pronamide may persist in soil. The half-life of the molecule is wholly dependent on soil temperature and moisture. At 10% soil moisture, Walker reported half-lives of 29 days at 23°C, 63 days at 15°C, and 140 days at 8°C. Reducing the soil moisture to 5% increased half-life by a factor of almost two at 23°C. Leistra et al. additionally found that the mobility of pronamide is slight beneath the top 5 cm of soil and is totally dependent on the breakdown kinetics of the herbicide.

Data submitted by Rohm and Haas on the hydrolysis of pronamide in water indicated that pronamide is relatively stable when the pH is nearly neutral. Little if any ^{14}C-pronamide was converted to $^{14}CO_2$. Other studies of pronamide in aqueous systems showed that it is slowly degraded by light and microorganisms in water and sludge (8).

D. Toxicology

On the basis of toxicological data submitted by Rohm and Haas, pronamide products are in Toxicity Category III (40 CFR 162.10) because pronamide exhibits only slight to moderate irritation to the skin and eye and has an acute toxicity in excess of 500 mg/kg. A complete chart of reported toxicological values is included in the Tables 2 and 3.

Since pronamide and most of its identified metabolites (3) contain an amide functional group with one amino hydrogen, the question of N-nitroso formation must be raised since N-nitroso compounds are extremely potent animal carcinogens. Dr. David Severn, Chemist, Chemistry Branch, Criteria and Evaluation Division (CED), stated "...pronamide could be nitrosated... This appears unlikely during manufacture...but could occur subsequent to application" (9).

The potential for N-nitroso formation is especially likely since some pronamide is marketed in a formulation with nitrogen fertilizers. N-nitroso formation may also

TABLE 2. Acute Toxicity of Pronamide Products

Test	Species, Sex	Product	LD 50
Oral	Rat-male	Kerb 75 WP (RH-315 75 WP)	4125 mg/kg
Oral	Rat-male female	Kerb - Technical (RH-315)	8350 mg/kg 5620 mg/kg
Oral	Rat-male female	Kerb - 50W (RH-315 50 WP)	16,000 mg/kg 16,000 mg/kg
Oral	Dog	Kerb - Technical (RH-315)	> 10 g/kg
Dermal	Rabbits	Kerb - Technical (RH-315)	> 3.16 g/kg
Dermal	Rabbits	Kerb - 50W (RH-315 50 WP)	> 10 g/kg
Primary skin irritation	Rabbits	Kerb 50W (RH-315 50 WP)	Not considered primary irritant at 0.5 g.
Percutaneous	Rabbits-male	Kerb 75 WP (RH-315 75 WP)	> 20 g/kg.
Eye Irritation	Rabbits	Kerb - Technical (RH-315)	Slight conjuntual redness at 3 mg; no corneal damage
Eye Irritation	Rabbits	Kerb 50W (RH-315 50 WP)	Slight irritant to unwashed eye at 100 mg.
Inhalation	Rats	Kerb 50W (RH-315 50 WP)	No mortality, but spots on lungs at 3.32 mg/l air.

Source: Section C of Pesticide Petitions 1F1139 and 9G0821.

TABLE 3. Wildlife Toxicity of Pronamide Products

Test	Species, Sex	Product	LD_{50}/LC_{50}
Oral	Japanese quail	Kerb 75 WP	8770 mg/kg
	male	Kerb 75 WP	9540 mg/kg
	female	Kerb 75 WP	8000 mg/kg
	Mallard duck	Kerb 75 WP	>14,000 mg/kg
Tank Water	Goldfish	Kerb 75 WP	LC_{50} = 350 ppm
	Guppies	Kerb 75 WP	LC_{50} = 150 ppm
	Rainbow trout	Kerb 75 WP	LC_{50} = 72 ppm
	Catfish	Kerb 75 WP	LC_{50} > 200 ppm
Treated Foliage (2 lb/ acre)	Honey bee	Kerb 75 WP	24 hr mortality = 0%
	Leafcutter bee	Kerb 75 WP	24 hr mortality = 5% (control = 4%)

Source: Section C of Pronamide Petitions 1F1139 and 9G0821.

occur after the pesticide is applied if there are nitrates present. This formation is therefore possible in soil, water, air, plants, and animals including man.

While some data show that pronamide does metabolize, the metabolites have essentially the same molecular structure except for the last two carbons. Thus it is unclear which part of the molecule is oncogenic. If the amide moiety of the molecule undergoes nitrosation to form an N-nitrosoamide, which is in a class of compounds shown to be potent oncogens in laboratory animals, then some pronamide metabolites may be oncogens. Moreover, there are no experimental data that demonstrate clearly that pronamide breaks down or is metabolized to harmless substances. Presence of CO_2 as a byproduct does not constitute sufficient evidence that this has occurred.

Other Rohm and Haas data show that pronamide is a low order toxicant in cold and warm water fish, waterfowl, and game birds. Pronamide had no effect on pollinating bees (10).

E. Uses and Production

Rohm and Haas is the only registered producer of technical grade pronamide and is also the largest formulator of pronamide products. Most of the technical grade pronamide manufactured and sold in the U.S. is formulated into Rohm and Haas Kerb 50 W (EPA Reg. No. 707-98). Rohm and Haas

produces most of the pronamide products registered for agricultural uses. Because production data are confidential, they are available for internal use within EPA only (Table 4).

Ornamental turf weed and grass control is the major nonagricultural pronamide use. All formulators hold registrations for this use. Pronamide is marketed in formulations for turf grass weed control in several concentrations and occasionally with fertilizers in the formulation as nutrients for the remaining grass. Other ornamental uses include weed control in commercial forest plantings. However, the use of pronamide on ornamental turf appears minor when compared to the agricultural uses.

Rohm and Haas exports approximately 200 tons of formulated pronamide each year. Use patterns abroad are similar to those in the United States. Countries to which pronamide is exported include Canada (alfalfa), South Africa (pasture management), Spain (citrus), Italy (orchard crops, lettuce), United Kingdom (beans, peas, lettuce), France (lettuce), and Japan (pasture management) (1).

Pronamide is available to the agricultural consumer in quantities sufficient to meet their demands. Rohm and Haas plans to develop additional uses for pronamide.

F. Alternative Pesticides

Alternative pesticides are registered for most of the uses and sites but not all the target organisms covered by pronamide registrations. Of the 41 alternatives currently identified, five are candidates for RPAR (three arsenicals, paraquat, and pentachlorophenol). In addition several other chemicals have been referred to the Office of Special Pesticide Reviews but have not yet been reviewed and accepted as candidates.

G. Human Exposure

Humans are most likely to be exposed to pronamide from the ingestion of treated lettuce. Residue data provided in the Rohm and Haas tolerance petitions for lettuce indicate that residues range from <0.01 to 1.8 ppm with a mean level of 0.3 ppm (10).

Other raw foods treated with pronamide which humans may ingest directly are cane fruits (blueberries, blackberries, boysenberries, and raspberries). Use patterns for these crops indicate that pronamide is applied in the winter and 100 days or more before berries are harvested for human consumption.

While alfalfa has the highest permissable pronamide tolerance of all raw agricultural commodities, the amount of alfalfa that humans consume directly is probably very small.

Residues from alfalfa are usually ingested via secondary routes of exposure: consuming meat, milk, and eggs of animals fed treated alfalfa. Levels of pronamide found in chickens fed field-aged alfalfa ranged from 0.02-0.09 ppm in the kidney <0.01-0.04 ppm in the liver, <0.01-0.02 in the gizzard, and <0.01-0.03 in fat (11).

Pronamide levels found after feeding cows alfalfa treated with pronamide also showed a wide variance. Concentrations in the liver varied from 0.02-0.17 ppm and those in the kidney were from <0.01 to 0.04 ppm. In a study performed in 1975, L. E. St. John and D. J. Lusk fed cows pure pronamide and found residues in milk ranging from 0.01-0.08 ppm (12).

FDA has not reported pronamide residues in samples from in their Market Basket Survey. However they have not been specifically examining food for pronamide residues (13).

II. Regulatory History

Since the first pronamide product was registered, there have been no restrictive or enforcement actions taken by EPA.

A. Tolerances

Registration Division has established the following tolerances for residues resulting from the direct application of pronamide: 10 ppm, alfalfa; 5 ppm, clover and forage

legumes; 2 ppm, lettuce and endive (escarole); 0.05 ppm, cane fruits (blackberries, blueberries, boysenberries, and raspberries).

The following tolerances for secondary residues resulting from feeding treated material to animals that produce meat, milk, and eggs were also established:

0.2 ppm	Kidney and liver of beef cattle, goats, hogs, poultry, horses, and sheep,
0.02 ppm	Eggs, milk, meat, fat, and meat byproducts (except kidney and liver) of cattle, goats, hogs, horses, poultry, and sheep.

A temporary tolerance based on an experimental use permit was granted for the use of pronamide on almonds, apples, apricots, cherries, grapes, nectarines, peaches, pears, pistachio nuts, plums, prunes, and walnuts. The experimental permit was for the 1974-75 growing season and was limited to 1500 lb pronamide. Rohm and Haas withdrew this permit in July 1976.

B. Previous EPA Reviews

On November 29, 1974, Mr. Robert Coberly of the Toxicology Branch, Registration Division (RD), reviewed an 18-month feeding study submitted with a tolerance petition

for alfalfa (14). Because of the increased frequency of hepatic carcinomas in male mice in this study, he concluded that pronamide might be a carcinogen (15).

On the basis of this evaluation Dr. Martin Rogoff, Pesticide Science Officer, RD, requested the opinion of Dr. Leonard Axelrod, Director, CED. In his reply dated December 18, 1974, Dr. Axelrod stated, "...we do not anticipate a human toxicological problem with carcinogenicty" (16).

Upon receipt of Dr. Axelrod's memo the Toxicology Branch, RD, reexamined the petition. In a review dated October 10, 1975, Mr. David Ritter, Pharmacologist reaffirmed Mr. Coberly's conclusion that pronamide may be a carcinogen (17). In his review Mr. Ritter stated, "The evidence submitted ...is very strong that (pronamide) is a potential human carcinogen...It does produce...cancers... in the mouse." The Registration Division referred pronamide to the Office of Special Pesticide Reviews for further study.

III. Summary of Scientific Evidence to Support Rebuttable Presumption on the Basis of Chronic Toxicity

40 CFR 162.11(a)(3) provides that a rebuttable presumption shall arise if a pesticide's ingredient(s), metabolite(s), or degradation product(s) meet or exceed (i) acute toxicity risk criteria relating to hazards to humans, domestic

animals or wildlife, or (ii) chronic toxicity risk criteria relating to oncogenic, mutagenic, and delayed toxic effects in man and/or test animals, or relating to population reductions in nontarget organisms or fatality to members of endangered species.

The Pronamide Working Group has concluded that pesticide products containing pronamide meet the chronic risk criteria relating to oncogenic effects in test animals set forth in this Section.

A. Chronic Feeding Study in Which Oncogenic Effects Were Observed

The Working Group recommendation to presume against pronamide because of its oncogenic effects is based on data presented in a chronic feeding study submitted with a petition for tolerances for alfalfa and fresh hay: "Eighteen Month Study on the Carcinogenic Potential of Kerb (RH-315; Pronamide) in Mice" (14). Rohm and Haas, who submitted the study, holds that the results indicate that pronamide is not a true carcinogen and does not represent a substantial hazard to humans. However, three groups within EPA have reviewed this data and each has concluded that pronamide is a carcinogen.

The first reviews occurred in 1974-75 when Toxicology Branch specialists in the Registration Division evaluated these petitions and concluded that pronamide was a

potential human carcinogen. (See discussion in section II B). Later, in connection with the current RPAR review of pronamide, a CED contractor, Battelle Memorial Laboratories, Columbus, Ohio, reviewed this data and concluded that pronamide is an oncogen (18). Dr. Robert Potrepka of CED stated, "Based on the assumption that an adequate histopathology.... was conducted ....it may be concluded that pronamide is a carcinogen in (C57BL/6) x (C3HAnf) F1 male mice (19). The EPA Carcinogen Assessment Group (CAG) also concluded that the study indicated that pronamide is a carcinogen. CAG wrote "The mouse study showed a statistically significant excess of liver carcinomas in males associated with a 78 week exposure to 1000 and 2000 ppm of pronamide in the Diet" (20).

Data from the chronic feeding studies upon which these conclusions are based are presented in Tables 5, 6, and 7. The data in Table 5 indicate that 19% of 100 mice ingesting 1000 ppm pronamide daily in the diet developed malignant tumors, and that 28% of 99 mice ingesting 2000 ppm pronamide developed malignant tumors. By contrast, malignant tumors were found in 8% of 100 control animals.

TABLE 5. Tumors at All Sites in Male Mice Ingesting Pronamide a/

Dose, ppm	Mice with Benign Tumors		Mice with Malignant Tumors		Total Mice with Tumors	
	No.	%	No.	%	No.	%
0	0/100	0	8/100	8	8/100	8
1000	0/100	0	19/100	19 b/	19/100	19
2000	1/99	1	28/99	28	29/100	29

a/ This table records the number of mice with tumors and not the total number of tumors. Thus a mouse with more than one tumor is counted only once.
b/ Three questionable tumors are not included.

The CAG review also noted other liver lesions found in male mice that included adenomatous hyperplasia, degeneration, hyperplasia, intrahepatic cholestasis, necrosis, and/or fatty change (Table 6). Mice which had cholestasis, an extremely rare lesion, did not have carcinomas of the liver. There were no lesions of the liver reported for female mice in the control group and only 1 and 2% in the liver of female mice ingesting 1000 and 2000 ppm pronamide, respectively (Table 7).

TABLE 6. Liver Lesions in Male Mice Ingesting Pronamide a/

Dose, ppm	Mice with Hyperplasia		Mice with Adenomatous Hyperplasia		Mice with Carcinomas		Total Mice with Lesions	
	No.	%	No.	%	No.	%	No.	%
0	0/100	0	0/100	0	7/100	7	7/100	7
1000	0/100	0	3/100	3 b/	18/100	18	21/100	21
2000	5/99	5	6/99	6 c/	24/99	24 d/	36/99	36

a/ Twenty-eight mice had intrahepatic cholestasis which were not tabulated. The number of mice in each group would be slightly higher if results were corrected for survival time.
b/ Includes two mice with questionable carcinomas.
c/ Includes two mice with questionable carcinomas.
d/ One mouse also had biliary cirrhosis.

TABLE 7. Liver Lesions in Female Mice Ingesting Pronamide a/

Dose, ppm	Mice with Adenomatous Hyperplasia		Mice with Carcinomas		Total Mice with Lesions	
	No.	%	No.	%	No.	%
0	0/100	0	0/100	0	0/100	0
1000	0/100	0	1/100	1	1/100	1
2000	0/99	0	2/99	2	2/99	2

a/ The number of mice in each group would be slightly smaller if results were corrected for survival time.

Metastases of the liver tumors were not observed in this study. CAG explained that because this study was terminated at 18 months, the animals had not lived long enough for metastases to develop. Therefore, although there were no reported metastases by the conclusion of the study, this data does not conclusively demonstrate that metastases would not have occurred if the study had gone to 24 months, i.e., the full life expectancy of the mouse. Moveover, CAG predicted that if the study had not terminated after 18 months and if known histological trends were followed, mice that had hyperplasia would most likely have developed carcinomas. CAG characterized the nonhepatic tumors as lymphomas.

In summary, both CED and CAG reported that pronamide increases hepatic carcinomas in male (C57BL/6 x C3HAnf) F1 mice. CAG also identified additional tumors which cannot be properly evaluated because of the method of tissue collection.

Thus the Working Group concludes that a rebuttable presumption against the registration of pronamide products should be issued based on its oncogenic potential as demonstrated in the Rohm and Haas 18-month mouse feeding study.

B. Chronic Feeding Studies Reporting No Oncogenic Effects

1. "Toxicologic Study on the Effect of Adding RH-315 to the Diet of Rats for a Period of Two Years"

Rohm and Haas fed groups of 30 rats pronamide in their diet at levels of 30, 100, and 300 ppm for 2 years (21). Results of the study are reported in Tables 8-11. Rohm and Haas concluded that no toxic effects were shown. CAG reported that male and female rats developed tumors in both the controland treated groups but that no trend or dose response relationship could be observed (20). The CED report noted the tumor formation but could not offer comment without a complete histopathologic reexamination. CED recommended that future feeding studies included a tissue residue analysis for proper assessment of potential toxic effects (19). For these reasons neither CED nor CAG could conclude that pronamide caused oncogenic effects. However, because CAG also noted that a reexamination of organs containing tumors would be worthwhile, the Agency has requested that Rohm and Haas submit slides of thse tissues for examination.

TABLE 8. Benign and Malignant Tumors in Male Rats Ingesting Pronamide a/

Dose, ppm	Rats with Benign Tumors		Rats with Malignant Tumors		Total Rats with Tumors	
	No.	%	No.	%	No.	%
0	2/22	9	0/22	0	2/22	9
30	3/22	14	1/22	5 b/	4/22	18
100	0/21	0	0/21	0	0/21	0
300	2/19	15	0/19	0	2/19	15

a/ Tumors of the mammary glands and pituitary are listed in another table and are not included here.
b/ Reticulum cell sarcoma of the lung.

TABLE 9. Benign and Malignant Tumors in Female Rats Ingesting Pronamide a/

Dose ppm	Rats with Benign Tumors		Rats with Malignant Tumors		Total Rats with Tumors	
	No.	%	No.	%	No.	%
0	1/22	5	0/22	0	1/22	5
30	0/17	0	0/17	0	0/17	0
100	3/22	14	0/22	0	3/22	14
300	4/21	19	1/21	5 b/	5/21	24

a/ Tumors of the mammary glands and pituitary are listed in another table and are not included here.
b/ Carcinoma of the uterus with metastases to the adrenals.

TABLE 10. Tumors of the Mammary Glands and Pituitary in Female Rats Ingesting Pronamide

Dose, ppm	Rats with Mammary Gland Tumors a/		Rats with Pituitary Tumors		Total Rats with Tumors b/	
	No.	%	No.	%	No.	%
0	12/22	55	6/22	27	15/22	68
30	9/17	53	4/17	24	12/17	71
100	11/22	50	4/22	18	13/22	59
300	11/21	52	1/21	5	11/21	52

a/ Tumors were described as fibromas or adenomas. This Table records the number of mcie with tumors and not the total number of tumors.

b/ Rats that had both types of tumors are counted only once in this column.

TABLE 11. Tumors of the Mammary Glands and Pituitary in Male Rats Ingesting Pronamide

Dose, ppm	Rats with Mammary Gland Tumors a/		Rats with Pituitary Tumors		Total Rats with Tumors	
	No.	%	No.	%	No.	%
0	1/22	5	2/22	9	3/22	14
30	1/22	5	0/22	0	1/22	5
100	2/21	10	0/21	0	2/21	10
300	2/19	11	0/19	0	2/19	11

a/ Tumors were described as fibromas or adenomas. This Table records the number of mice with tumors and not the total number.

b/ Rats that had both types of tumors are counted once in this column.

2. "Toxicologic Study on the Effect of Adding RH-315 to the Diet of Beagle Dogs for a Period of Two Years"

This study, which was submitted by Rohm and Haas (22) could not be used to assess oncogenic or other chronic effects since the dogs were fed pronamide for only 2 years which is not "the greater part of the animal's life span" as required by the National Cancer Institute guidelines. In addition the number of animals tested was small. Dr. Robert Potrepka of CED concluded "...with the sacrifice of one dog at the end of one year statistical differences would be difficult to obtain with only the remaining animals of each sex per dose" (20). The CAG report on this study reached the same conclusion. Therefore, EPA will not request the opportunity to reevaluate these tissue slides.

LIST OF APPENDICES

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